Bayer 9265-LH

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Hubert Dorn et al.
Serial No.:	08/440,428
Filed:	May 12, 1995
For:	NON-SYSTEMIC CONTROL OR PARASITES
Group:	1209
Examiner:	A. Robinson

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION

Dr. Hubert Dorn of Pahlkestrasse 71, 42115 Wuppertal, Germany, hereby declares :

- that he is a veterinarian having studied at the Universities of Hannover and Giessen;

- that in 1970 he received his doctor's degree at the University of Hannover;

- that in 1970 he entered clinical development department of business group animal health of Bayer AG;

- that in 1990 he became head of clinical development for pet products and in 1992 he became head of clinical development for livestock and pet products of Bayer AG's animal health business group;

- that he is one of the inventors of the present application;

- that he is declarant of the declaration in this case of August 4, 1996,

- that under his supervision product development work for flea combatting products for cats and dogs has been conceived, planned and carried out either within Bayer's research and development facilities or with outside research groups;

- that under his supervision clinical development of Bayer's insecticide Imidacloprid as a flea combatting product for cats and dogs has been carried out;

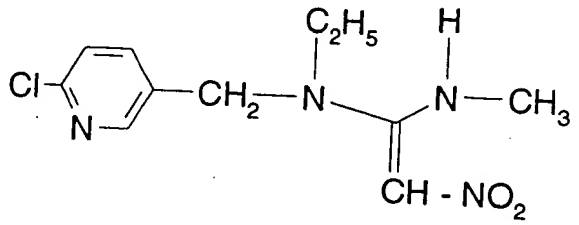
- this part of his work was directed to comparison with products of other companies either already on the market for this use or also under development;

- that the following investigation has been carried out under his guidance and supervision;

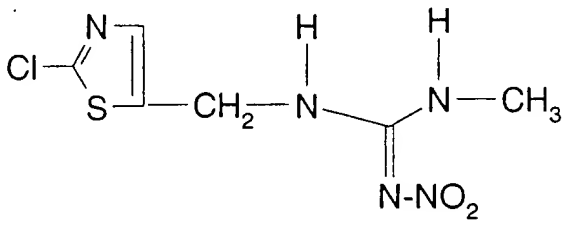
- the aim of this investigation was to compare the activity and tolerance of spot-on formulations of three chloronicotinyl derivatives using cats as the target animals.

- as chloronicotinyl derivatives the following compounds have been used:

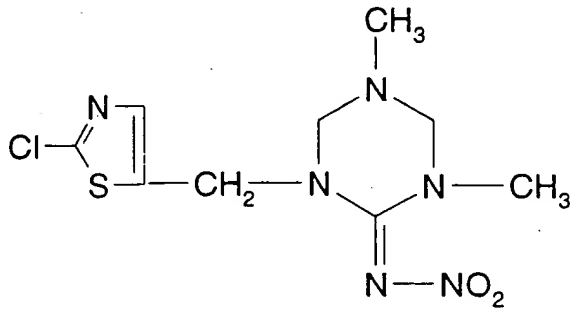
1. Ti 304 of the formula



2. Ti 435 of the formula



3. AKD 1022 of the formula



Materials and methodology:

Fifteen cats were divided into five groups of three animals. All the animals of each treatment and control group were infested twice before treatment (day -6, -4) and then at weekly intervals (day 7, 14, 21 and 28) with approximately 100 less than four-week-old live fleas. The activity test was carried out 48 and 72 hours after the treatment and 48 and 72 hours after each infestation by means of the semiquantitative determination (0 to +++) of the flea eggs which fell from the animals within a specific period of time (2 hours) on to photographic cardboard placed underneath the cages.

In addition, the flea eggs were incubated in order to assess whether they develop into adult fleas. The incubation will be complete on 28.11.96.

The test substances were applied once by spot-on administration on day 0. The aim was to apply the active compounds in a dose of 10 mg/kg body weight. Subsequent analysis did however reveal a different content of the active compounds in the individual formulations.

Thus one test group was treated with a 7.7% formulation of TI 304, one test group with an 8.1% formulation of TI 435, and an additional test group with a 4.09% formulation of TI 435. A fourth test group was treated with a 7.2% formulation of AKD 1022. In addition, this formulation contained 1.05% of TI 435, a decomposition product of AKD 1022. A fifth group was used as an untreated control.

The exact dosages are summarised in Table 1.

Table 1: The actual content of active compound and the exact dosages of the spot-on formulations

test group	formulation	content of active compound	dosage [mg/kg]
1	SYK 3514	7.7% TI 304	7.7
2	SYK 3515	8.1% TI 435	8.1
3	SYK 3517	4.09% TI 435	8.18
4	SYK 3516	7.2% AKD 1022 1.05% TI 435*	7.2 AKD 1022 1.05 TI 435*
5	/	/	/

*According to analysis the formulation SYK 3516 contained 1.05% of TI 435, a decomposition product of AKD 1022

For the examination of tolerance, the cats were subjected to a general clinical examination at specific time intervals before and after the treatment.

Results

The substances are considered to be fully active if no flea eggs are collected. If flea eggs are however found this is referred to in the following as unsatisfactory.

Apart from in one cat in test group 2 (SYK 3515, TI 435) all the formulations were fully active up to and including day 24. As from day 30 unsatisfactory activity was found in one cat in each of test groups 1, 2 and 4.

TI 304 (test group 1)

Three days after the spot-on treatment with 7.7 mg/kg body weight of TI 304, full activity was displayed in two out of three cats. On the other hand, in the third cat the formulation still only displayed unsatisfactory activity on the third day. From then on up to day 24 after the treatment full activity was displayed in all three cats of test group 1, and in two cats the formulation was fully active up to the end of the test (day 31). In one cat a small number of flea eggs was found on day 30 and 31 and the activity was thus unsatisfactory.

TI 435 (test group 2)

Three days after the treatment with 8.1 mg/kg body weight of TI 435 full activity was displayed in all the cats of test group 2. The formulation remained fully active in two cats up to the end of the test (day 31). In one cat the activity was no longer satisfactory as from day 16.

TI 435 (test group 3)

Three days after the treatment with 8.18 mg/kg body weight of TI 435, unsatisfactory activity was still displayed in two out of three cats. From then on up to the end of the test on day 31 the formulation was fully active in all three cats of test group 3.

AKD 1022 (test group 4)

The spot-on treatment was carried out with 7.2 mg/kg body weight of AKD 1022 and 1.05 mg/kg body weight of TI 435. After the treatment, full activity was displayed in one cat up to the end of the test (day 31). In one cat the formulation still displayed unsatisfactory activity on the second day, although full activity was then displayed up to day 31. In one animal in this test group unsatisfactory activity was displayed on day 3 and then again on day 30 and 31.

Control (test group 5)

A moderate to high number of flea eggs was collected from all the cats in the control group. In one cat only on day 9 were no flea eggs collected, and on day 10 only a small number of flea eggs fell from this cat.

A summary of the results is given in Table 2.

Table 2: Results of the collection of flea eggs before and after treatment with various spot-on formulations

test group	animal no.	flea eggs on day -1	2	3	9	10	16	17	23	24	30	31	full activity in x/3 cats up to day 31
1	023			0	0	0	0	0	0	0	0	0	2
	RVZ 17		0		0	0	0	0	0	0	0	0	
	KNB 9206			0	0	0	0	0	0	0			
2	041			0	0	0							2
	KNB 9528		0	0	0	0	0	0	0	0	0	0	
	KNB 9531			0	0	0	0	0	0	0	0	0	
3	KNB 9340			0	0	0	0	0	0	0	0	0	3
	941360				0	0	0	0	0	0	0	0	
	RVX 38				0	0	0	0	0	0	0	0	
4	RVX 23		0	0	0	0	0	0	0	0	0	0	2
	RVX 50				0	0	0	0	0	0			
	KNB 9212			0	0	0	0	0	0	0	0	0	
5	KNB 9519				0								/
	941347												
	RVX 40												

flea eggs on day — full activity in x/3 cats up to day 31

test group — animal no.

flea egg count: + = 1 - 10 flea eggs
++ = 11 - 100 flea eggs
+++ = > 100 flea eggs

Tolerance

In the general clinical tests carried out the formulations applied in this test did not produce any symptoms of intolerance.

Development control

The development control is not yet complete. It can however already be said at the present time that the chloronicotinyl derivatives tested have larvicidal activity. The final results are discussed in the final report.

Discussion

The formulations of TI 304, TI 435 and AKD 1022 used in this test displayed a delayed onset of action, since in each test group full activity was not displayed up to day 2 after the treatment in at least 2 out of three animals. In the case of TI 435, on comparing test groups 2 and 3 a difference between the formulations from the point of view of a delayed onset of action can be detected, although the difference between the doses of these groups is minimal and thus negligible. Whereas in all three cats of test group 2 (SYK 3515) full activity was displayed on the third day, full activity was still not displayed on day 3 in test group 3 (SYK 3517) in two out of three animals. TI 435 acts more quickly (has a more powerful "knock-down effect") in the SYK 3515 formulation than in the SYK 3517 formulation.

Formulations SYK 3514 (TI304) and SYK 3516 (AKD 1022, including the decomposition product TI 435) have a similarly longlasting effect, since a small number of flea eggs only fell from one out of three cats on day 30.

In test group 2 (SYK 3515, TI 435) the cessation of activity in one cat as early as day 16 can only be explained speculatively. It is possible that this cat licked off the medicament after administration, thus leading to a reduction in activity.

In formulation SYK 3517, TI 435 has the best longterm effect of the formulations tested. The formulation was fully active in all the cats after day 3 up to the end of the test (day 31).

Due to the very precise method used for the collection of the flea eggs, the formulations of TI 304, TI 435 and AKD 1022 used in this test can be described as having excellent adulticidal and larvicidal activity against fleas over a period of 31 days. These formulations also display very high tolerance.

The undersigned declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Hubert Dorn

Hubert Dorn

10.12.96

Date